B 2
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24. (Once amended) An isolated ~~single chain~~ anti-botulinum neurotoxin type A (anti-BoNT/A) antibody, ~~said antibody~~ comprising a variable heavy (VH) complementarity ~~determining~~ region (CDR) listed in Table 4 and wherein said antibody ~~specifically~~ binds to and neutralizes a botulinum neurotoxin type A.

REMARKS

Status.

Claims 1-43 are pending with entry of this amendment, claims 44-77 being cancelled and no claims being added herein. Claims 1 and 24 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification (*e.g.*, pages 17-19, example 1, *etc.*).

Election/Restriction.

Applicants note that the restriction requirement designating Groups I-IV is made final. Accordingly, non-elected claims 44-77 are canceled herein. Please note, however, that Applicant reserves the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Information Disclosure Statement.

Applicants note that the Examiner has indicated that she has considered the items listed on form PTO-1449 (references C1-C12). Applicants thank the Examiner for her thorough review of these references.

35 U.S.C. §112, second paragraph.

The Examiner rejected claims 6-10, and 17-43 as allegedly indefinite for using the phrase "variable heavy complementarity determining regions (CDRs) listed in Table 4" and for using the phrase "variable light complementarity determining regions (CDRs) listed in Table 4". In addition, claims 17-21 were rejected as allegedly indefinite for reciting the phrase "framework region regions in the antibodies VH region and VL region listed in Table 4". In particular the Examiner alleged that the sequences are not clearly defined by the specific sequence or by the specific property and characteristic. Applicants respectfully traverse.

Table 4 expressly provides complete amino acid sequence information for Framework 1, CDR1, Framework 2, CDR2, Framework 3, CDR3, and Framework 4 for the VH region and the VL region of every clone identified therein. Moreover, Table 4 uses dashes "-" to identify amino acids common to the all the listed sequences that bind to each particular epitope and amino acid designations to expressly illustrate how various sequences that bind to a particular epitope differ from each other.

Because a complete amino acid sequence is proved for every VH or VL Framework region and/or CDR recited in the claims the Examiner is incorrect in his assertion that the above-identified claim language is indefinite. Accordingly, the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

The Examiner also rejected claims 2-5, 11, and 30 under 35 U.S.C. §112, second paragraph, as allegedly indefinite stating that "it is not clear which antibody the applicant intent [sic] to indicate since there are two different antibodies in claim 1 an isolated antibody and an antibody expressed by a clone." Applicants respectfully traverse.

It is well accepted that antibodies can and are described structurally and/or by the epitope to which they bind. Claim 1 is directed to:

> 1. An isolated single-chain antibody **that specifically binds to an epitope specifically bound by an antibody expressed by a clone selected from the group consisting of clone S25. . . "**

The recitation of the particular clones in claim 1 is to specifically characterize the binding specificity of the claimed antibody. In other words, claim 1 is directed to isolated single chain antibodies that are cross-reactive with the particular recited clones. This, of course, includes the recited clones since antibodies are cross-reactive with themselves.

There simply is no ambiguity with respect to which antibody claims 2-5, 11, and 30 refer. The rejection of these claims under 35 U.S.C. §112, second paragraph, is improper and should be withdrawn.

35 U.S.C. §102.

35 U.S.C. §102(b).

Claims 1-11, 13-14, 17-30, 32-33, 36-43 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Atassi *et al.* (1996) *J. Prot. Chem.*, 15(7): 691-699). Applicants respectfully traverse.

The Examiner is respectfully reminded that anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." *Kalman v Kimberly-Clark Corp.*, 218 USPQ 781, 789 (Fed. Cir. 1983). In the instant case, independent claims 1 and 24 are amended herein to recite:

> "1. An isolated **single-chain** antibody. . ."; and
>
> "24. An isolated **single chain** anti-botulinum neurotoxin type A (anti-BoNT/A) antibody. . . "

respectively. In contrast, Atassi, *et al.* only discloses the creation of native (*i.e.*, double-chain) antibodies. Thus, for example, Atassi *et al.* states:

> Horse antisera were prepared by immunization subcutaneously in multiple sites and every 2 weeks for over 1 year, with a formaldehyde inactivated BoNT/A in Biri adjuvant. (Atassi *et al.* page 693, col. 1)
>
> * * *
>
> Human antisera were made against the pentavalent toxoid in human volunteers as described . . . (Atassi *et al.* page 693, col. 1)

Atassi *et al.* offers no teaching whatsoever of a single-chain antibody directed against a botulinum neurotoxin. Accordingly, Atassi *et al.* fails to disclose a limitation of the presently claimed invention and therefore does not anticipate this invention. Accordingly, the rejection under 35 U.S.C. §102(b) should be withdrawn.

35 U.S.C. §102(a).

Claims 1-43 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Amersdorfer *et al.* (1997) *Infect. Immun.*, 65(9): 3743-3752. Applicants respectfully traverse.

The Examiner is reminded that anticipation under §102(a), requires that the invention be "known or used by others in this country, or patented or described in a printed publication in this or a foreign country, **before the invention thereof** by the applicant for patent." In the instant case, it is noted that the Amersdorfer reference described Applicant's own work. James D. Marks and Peter Amersdorfer are both listed as authors on the subject reference. Applicants' could not have published on their own work prior to its discovery/invention. Thus, Amersdorfer *et al.* was not published before the invention thereof by the Applicants and the rejection under 35 U.S.C. §102(a) should be withdrawn.

35 U.S.C. §103(a).

Claims 1-43 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Atassi *et al.* (1996) *J. Prot. Chem.*, 15(7): 691-699 taken with Emanuel *et al.* (1996) *J. Immunol. Meth.*, 193: 189-197. According to the Examiner, while Atassi *et al.* allegedly teaches intact "native" anti-botulinum neurotoxin type A antibodies (anti-BoNT/A) they do not teach or suggest a single-chain antibody. Emanuel *et al.* is cited as allegedly teaching single chain anti-BoNT/B antibodies. The Examiner then argued that it would be obvious to use the method taught by Emanuel to generate single chain antibodies against the antigen taught by Atassi *et al.* Applicants respectfully traverse.

The Examiner is reminded that *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger, 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987).* Moreover, to support an obviousness rejection, the cited references must additionally provide a reasonable expectation of success. *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.,* 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In the instant case, Applicants first note that, as explained below, Emanuel *et al.* does not disclose an anti-BoNT/A antibody. In addition, Applicants explain that under prevailing law, it is improper to consider the method of making in formulating an obviousness rejection. It is well established that a general **method** of making does not render obvious a claimed composition.

A) Emanuel *et al.* does not disclose anti-BoNT/A.

First Applicants note that, contrary to the Examiner's assertion, Emanuel teaches the production of an anti-botulism neurotoxin **type B** antibody (anti-BoNT/B) not an anti-BoNT/A. As shown in Emanuel *et al.*, Table 1, **the only neurotoxin (NT) specific antibodies produced were specific to neurotoxin B, not to neurotoxin A**.

B) It is improper to consider method of making the antibodies.

In formulating his rejection, the Examiner improperly considered the method of making the claimed antibodies. In effect, the Examiner alleged that because **methods** to make single chain anti-BoNT/B antibodies, the particular antibodies recited in claims 1-43 would have been obvious in light of these methods. The courts have specifically rejected this

basis for rejecting claims (*see In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1994) and *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995)). In both cases, the PTO alleged that composition claims directed to nucleic acids were obvious in view of references that taught general methods for making oligonucleotides and then using them to isolate desired nucleic acids. In *Deuel*, the Federal Circuit reversed the PTO, reasoning that:

> The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. . . . **We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.** [emphasis added] *Deuel*, 51 F.3d at 1555.

Here, as in *Bell* and *Deuel*, the Examiner argues that the claimed antibodies are obvious in light of a general method for making single chain antibodies and an alleged disclosure of suitable epitopes. The Examiner has failed to show how the cited references provide any specific information about the particular claimed antibodies. To the contrary, the cited references provide no teaching or suggestion of antibodies cross-reactive with the antibodies listed in the Markush group of claim 1, or comprising the particular CDRs identified in claim 24. Furthermore, the cited art not only fails to teach or suggest antibodies having the binding specificity of the presently claimed antibodies, but also fails to teach or provide a reasonable expectation that antibodies having such particular binding specificities would also be neutralizing antibodies.

Since the cited references neither disclose nor suggest the existence of the particular claimed antibodies and the Federal Circuit has stated that consideration of a general method of discovery is an improper basis for an obviousness rejection, Applicants submit the Examiner has failed to make his *prima facie* case. Accordingly, the rejection of claims 1-43 under 35 U.S.C. §103(a) should be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 217-6021.

Respectfully submitted,

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Encl: 1) Petition for 3 month extension of time.
2) Change in correspondence address.